MedicalXpress

Alterations in gene regulation make gastric cancer cells less visible to the immune system

October 19 2017

Gastric cancer cells are helped to evade the immune system by alterations in gene regulation, according to new work by A*STAR researchers. This mechanism might apply to a wide range of cancers, and could be exploited to improve cancer treatments.

Gastric cancer is among the most common and deadly forms of the disease and has limited treatment options. The impact of gastric cancer means that its genetics have been studied extensively. Patrick Tan, from the A*STAR Biomedical Research Council, and an international research team now provide new insight by studying variation in gene promoters, components of DNA that regulate gene expression.

"Promoters act as multifaceted switches that turn genes on or off, regulate the amount of gene expression and control a gene's output," explains Aditi Qamra from the A*STAR Genome Institute of Singapore, primary author of the study. "More than half of the genes in the human body have more than one promoter controlling them, and cancer cells often exploit this by using abnormal promoters to drive malignancy. We wanted to identify which promoters are abnormally activated or silenced in gastric cancer cells."

The researchers used a technique called Nano-ChIP-Seq that uses molecular tags on histones—proteins that DNA molecules are wrapped around—to locate and identify active gene promoters. Comparing active promoters in gastric cancer cells with those in healthy gastric cells enabled identification of almost 2,000 promoters that are altered in

gastric cancer.

The alterations in promoters not only conferred cancerous properties, but also reduced the expression of proteins in tumor cells that would enable the immune system to detect them. This mechanism helps the cells evade the immune system, but also reduces the effectiveness of immunotherapy, which exploits the immune system to attack the tumor. Ultimately, the findings could be used to improve treatment.

"Studying the tumor promoter profiles of gastric cancer patients can help to identify suitable candidates for immunotherapy," explains Qamara. "Also, the reversible nature of promoter activity can be exploited to modulate the immunogenicity of gastric cancer tumors and make them more sensitive to immunotherapy."

Furthermore, analysis of a cancer genetics database revealed many similar promoter alterations in other cancers—colon cancer, kidney renal clear cell carcinoma and lung cancer—suggesting that similar mechanisms apply to many cancers. The researchers now aim to determine the cellular pathways involved in the function of the altered promoters. "Targeting these pathways can potentially increase the response rates of gastric cancer patients to immunotherapy," says Qamra.

More information: Aditi Qamra et al. Epigenomic Promoter Alterations Amplify Gene Isoform and Immunogenic Diversity in Gastric Adenocarcinoma, *Cancer Discovery* (2017). DOI: 10.1158/2159-8290.CD-16-1022

Provided by Agency for Science, Technology and Research (A*STAR), Singapore